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# THROMBOEMBOLIC DISEASE

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# Contents

# THROMBOEMBOLIC DISEASE

*The search for truth is in one way hard and in another easy. For it is evident that no one can master it fully nor miss it wholly. But each adds a little to our knowledge of Nature and from all the facts assembled there arises a certain grandeur.*

ARISTOTLE

# I

# Introduction*

DIFFERENCES of concept of the factors which bring about clotting of blood within the vascular tree, have brought about a wide fluctuation of therapeutic emphasis in the past Emphasis has been placed on: (1) exercises in bed; (2) early ambulation; (3) elastic compression; (4) postoperative Trendelenburg position, (5) any other method to speed venous return from areas of stasis, and (6) the detection, prevention and treatment of abnormal clotting tendency in the postoperative state

The injury to the non-wettable intima, whether the injury is mechanical, thermal, or immunological, has perhaps received the least attention The vascularity of vessel walls, the apoplexy of atheromatous plaques, the changes in intimal wettability, and the physical interaction between cellular elements of the blood and the lining walls, have intrigued many an experimental pathologist. Their work forms an important trend in the study of vascular diseases.

It is distinctly not the purpose of this report to get lost in the maze of data which has accumulated both in preclinical and clinical sciences on this subject.† Even the nomenclature used by the "coagulationists" (a horrible term only sanctified by common usage) is such that much time is spent defining what the participants of conferences on blood clotting are talking about.[1]

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* Aided in part by a grant of the Chicago Heart Association

† The difficulty of evaluating prophylactic and therapeutic measures for thromboembolism has recently been emphasized by Dr De Bakey's collective review in *Int. Abst. Surg.*, *98* 1, 1954

Surgeons are facing a daily problem in the management of thromboembolism. Undoubtedly, the progress which is needed will come from the basic sciences. It is well to remember, however, that two *surgeons*, Crafoord and Gordon Murray, were the pioneer contributors to anticoagulant therapy.[2]

In the following pages we will discuss the methods used in our service to manage thromboembolic disease. Our service is daily subjected to the impact of newer concepts and newer methods. It is interesting to note however that our original belief in the basic importance of the role of the clotting mechanism has not suffered any drastic revision.

The cerebral, coronary, pulmonary or calf muscle infarct have the same pathologic and physiologic characteristics. Therefore each requires the same type of treatment. This will necessitate inter-departmental cooperation. Vascular surgery is but one of the specialties which has created uneasiness in some surgical groups. The feeling persists that there is overspecialization but this specialty should create an excellent opportunity to lessen that feeling. The study of thromboembolic phenomena indicates a fruitful trend of synthesis. It is a field which integrates a number of preclinical and clinical specialties under a common focus. Thus a healthy regeneration, not a fragmentation, of medical knowledge ensues.

Throughout this discussion, statistical data will be held to a minimum and should be interpreted with the utmost caution. The author believes that the accurate compiling of data by one group of workers, over a period of years, is preferable to joint mass-statistics. It is his feeling that in the latter instance impeccable statistical analyses may be frustrated by faulty data, uncontrolled variables, and confusion of criteria.

II

# Clinical Forms of Thromboembolism

It is a well-known fact that a clot may form in any part of the vascular tree and be clinically unrecognizable. These "silent" clots may occur in the brain, the heart, the lung, the peripheral arteries, or in the veins. In a general sense, they are short thrombi with sufficient collateral circulation to compensate for the vascular occlusion. Their significance lies in the fact that they serve as a nidus for propagation of the clot. This happens when: (1) blood pressure falls; (2) when direct trauma to the vessel occurs, or (3) when an increased tendency to clotting develops. One can then differentiate, with the naked eye and the microscope, the old organized thrombus and the fresh, soft, nonadherent tail which floats in the bloodstream.

An arterial clot will produce an infarct, anemic or hemorrhagic, dependent on available arterial collaterals and venous drainage. The venous clot will produce: (1) stasis; (2) increase in venous pressure; (3) edema, and possibly (4) capillary hemorrhage. In the following paragraphs, some of the common sites of such occlusion will be described briefly, but the perverted physiology remains the same.

**Cerebrovascular Accident.** Our procedure for treating this condition has recently been summarized.[8] The differential diagnosis between embolism, thrombosis, and hemorrhage is often impossible. Of first importance is whether the cerebral infarct is anemic or hemorrhagic.

ger of this complication. No patient should be subjected to this procedure for at least six months after a cerebral infarct.

**Cerebral Venous Thrombosis.** A typical course of events consists of hemiplegia following puerperium, accompanied by convulsions, papilledema, and a minimal amount of blood in the spinal fluid. This differs from an ascending thrombophlebitis from ear, nose, throat, and sinuses.[10] In nearly all of the cases of obstetrical longitudinal sinus thrombosis, there was evidence of venous thrombosis elsewhere in the body. J. P. Martin[11] was the first to designate the vertebral venous system as the ascending pathway to the cerebral sinuses in thromboses of this sort. Both of our cases had transitory spinal cord symptoms.

Anticoagulant therapy should not be employed when venous outflow is obstructed because of the tendency to petechiae and coalescing hemorrhages in the central nervous system. Anything that will diminish cerebral edema, such as concentrated albumen or cervical sympathetic block, is worthy of trial. In one of our cases treated by sympathetic block we have observed a complete functional recovery from a massive hemiplegia and aphasia following "puerperal hemiplegia."

**Vertebral Vein Thrombosis.** Coelho and the author[12] presented three case histories which included the coexistence of three significant findings. These were: (1) a demonstrable venous thrombosis in the lower extremities or pelvis; (2) marked strain or compression of the lower abdominal organs, notably the vena cava, and (3) the appearance of cord-symptoms of unknown origin. The latter produced transient spinal block, a non-pulsating dura on laminectomy, and a gradually receding level of paraplegia. We could offer no morphologic proof for the tentative diag-

nosis of vertebral vein thrombosis. However, the roentgenology department recently visualized the vertebral venous plexus by injecting opaque substance through the spinous process.[13]

Since the original reports of Batson,[14] the role of the venous system in the spread of carcinomatous metastases and pyogenic abscesses has been repeatedly emphasized. It may be significant that spinal cord lesions have not been reported before in cases of iliofemoral and pelvic vein thromboses. Obstruction of the vena cava was necessary, however, to force opaque material into the vertebral veins in living monkeys

There are a number of patients with vague sensory symptoms, and motor weakness, following an acute deep venous obstruction. Their complaints, however, were thought to be due entirely to reflex vasospasm. We can make no suggestions for therapy except neurosurgical exploration. This was done in one of our cases. Anticoagulants, it must be remembered, may precipitate hematomyelia Paravertebral sympathetic block was done in one of our cases, with no effect. The scattered fiber degeneration produced by ligating certain veins in the monkey cannot be prevented. However, the complete flaccid paraplegia recedes.[15] It will undoubtedly be the neurosurgeons and/or orthopedic surgeons who will lead the investigation of this syndrome in the future.

***Pulmonary Arterial Obstruction.*** *Pulmonary* artery thrombosis is quite rare, compared to pulmonary embolism. Little need be said about it except that in certain pulmonary infarctions where a complete autopsy fails to reveal the source of embolism, a thrombosis in situ must be considered. In 1934, Fowler[16] collected sixty cases from the literature. The classic description of W S. Middleton is of sur-

gical interest. He pointed to agonizing lower abdominal and epigastric pain, with collapse, as an unusual and startling manifestation of pulmonary thrombosis.[17]

Great clinical interest is focused on pulmonary embolism because of the wide disagreement as to the mechanism of production and the methods of its management. Preventive measures will be discussed under the heading of "Venous Thrombosis."

The incidence of pulmonary embolism has not changed appreciably despite the attention which has been devoted to it.[18] Pulmonary embolism occurs in at least four recognizable forms.[19] The four clinical forms of pulmonary embolism are: (1) the suspect, or subclinical embolus; (2) the small pulmonary infarct; (3) the massive sublethal pulmonary embolus, and (4) the fatal pulmonary embolus.[19] Dependent on the awareness of the hospital staff, and possibly on climatic conditions,[20] its incidence varies considerably in different institutions. Stroembeck[21] pointed out that with improved pre- and postoperative care, the incidence of thromboembolic disease has been lowered to one-third of its previous frequency. The present care consists of: (1) early systematic motion in bed; (2) elevation of the foot of the bed for better venous drainage; (3) early ambulation; (4) correction of blood loss; (5) dehydration, and (6) hypoproteinemia. The lowering of frequency has been brought about without the use of prophylactic vein-ligations or anticoagulant therapy.

A noticeable increase in frequency has been noted in the aged. This has been brought about by the increase of extensive surgery in the cardiovascular cripple and for carcinomatosis.[22] Better surgical care and more extensive surgery, as opposing influences, may nullify the advantages of the one by increasing the incidence through the other. A minimal irreducible incidence of pulmonary embolism seems to

remain about 0.1 per cent of all major surgical procedures. There may be an over-all incidence of 0.5 to 1 per cent thromboembolic phenomena.

It should be emphasized that the majority of all emboli occur before any peripheral venous, or cardiac source of embolism is known or suspected. Therefore, it seems inappropriate to take specific prophylactic measures, such as femoral vein ligation or anticoagulant therapy, before every major operation. Furthermore, there is a considerable incidence of post-traumatic pulmonary embolism. This is especially noticeable after fractures of the hip and pelvis which necessitate prolonged disability, due to postphlebitic sequelae. Anticoagulant therapy has for years been our standard treatment for spreading thrombosis when it is recognized early.

The rapidly fatal pulmonary embolus, which kills the patient in a period from a few minutes to one-half an hour, defies all known treatment. Many investigators postulate that such cases represent a massive total obstruction of the pulmonary artery This would lead to syncope and immediate right-heart failure. Beck, Fenn, and the author, in 1939, presented evidence from the literature and from personal clinical and experimental data showing that patients may die of small peripheral arterial emboli with an intensive autonomic nervous reflex [23] These small emboli may result in vagal inhibition of the heart, decrease in coronary flow, vasospasm of the uninvolved branches of the pulmonary artery, bronchospasm, and increased bronchial secretion leading to atelectasis.[24] With today's angiocardiography and cardiac catheterization, many of these earlier experiments seem crude by comparison Nevertheless, many subsequent studies have failed to prove that autonomic and vagal reflexes do not play a part in sudden death due to pulmonary embolism. There is strong evidence, recently reported, that

autonomic reflexes, particularly during hypoxia, are active and explain many of the clinical symptoms. Trigger zones of these reflexes are found in the visceral pleura, in ischemic lung, in pulmonary arterial hypertension, and in patches of ischemic myocardium

*In the acute crisis of pulmonary embolism*, the patient dies of acute right heart failure and failure of adequate venous return to the left heart. This, in turn, causes a fall in aortic pressure.[25] Therefore, every effort should be made to lower the increased pulmonary arterial pressure proximal to the obstruction. Kaunitz and Anderson[26] have shown that complete parasympathetic denervation of both lungs produces a decrease in pulmonary arterial pressure, averaging 46.5 per cent, in the experimental animal.

The customary doses of atropin (1/150 gr.) are inadequate to produce such an acute vagal interruption. Jesser and the author[27] suggested 1/75 gr. to 1/60 gr., intravenously. It is believed doses of this size may accomplish sufficient acute vagal interruption in the first few hours of pulmonary embolism to save the patient. Recent interest in cardiac arrest has caused us to increase the preoperative doses of atropin to a minimum of 1/100 gr. to 1/75 gr. No noticeable increase in side-effects from the drug have been noted. When the diagnosis of pulmonary embolism has been made or suspected—and much of the burden is on a specially-alerted nursing staff—the following emergency measures are instituted:

(1) *Oxygen*, by mask or tent, to relieve hypoxia, cyanosis and dyspnea.

(2) *Atropin*, intravenously (1/75 gr. to 1/60 gr.), repeated two to three times in the first twenty-four hours to dampen parasympathetic reflexes.

(3) *Papaverine*, intravenously (½ gr.), to combat bron-

chospasm and decrease cardiac irritability which may lead to ventricular fibrillation.

Some patients die suddenly from pulmonary embolism. However, the majority recover after one to several hours. The slowly fatal pulmonary embolism[28] causes the patient to exhibit a gradually falling arterial pressure and a rising venous pressure, over a period from hours to days. This symptom is a definite indication for pulmonary embolectomy through the right ventricle.[29] This is a very infrequent situation and we have had no personal case in which it was manifest However, it should be kept in mind as a possibility. When a patient holds his own, or shows some sign of improvement, anticoagulant therapy should be started. At the same time the source of the embolus should be investigated as closely as possible. Frequently, an extension into the popliteal vein of an obscure thrombus in the calf muscles requires several days after the occurrence of pulmonary embolism. Not infrequently, a diagnosis of "virus pneumonia with postpneumonic thrombosis" is made in these cases

If the source of an embolus is definitely in the calf muscle, and if the embolus is massive, a second embolus might be fatal. Treatment should consist of division of the superficial femoral vein followed by anticoagulant therapy. The latter is used to prevent ligature thrombi and keep the profunda femoris open. The decision is more difficult when evidence of common femoral vein obstruction is present. In such cases, aspiration of the clot, followed by anticoagulant therapy, is indicated [27,30] Common femoral vein ligation proximal to the entrance of the saphenous vein should be avoided in every instance except prior to amputation This procedure can easily result in permanent edema.

After a non-fatal attack of pulmonary embolism, there is

a marked tendency to recurrence. For this reason, anticoagulant therapy should be continued for three to four weeks. Another source of difficulty is the development of arterial stenosis at the site of organizing emboli. This may lead to *secondary thrombosis.*[31] Maintenance of adequate cardiac action and anticoagulant therapy are the logical measures to counteract this complication.

Many patients, especially on medical services, are placed on dicumarol therapy following pulmonary embolism. The difficulties, disadvantages, and dangers of this therapy will be discussed below. The dicumarolized, sometimes bleeding, patient may continue to produce emboli. Usually, *when seen by the surgeon, the thrombosis has extended to* the iliofemoral segments on one or both sides. In these patients, restoration of the prothrombin level followed by vena cava ligation is imperative.

Coronary Thrombosis. To the casual observer, this might seem to be an unusual subject to be included among the clinical forms of thromboembolism encountered by surgeons. Obviously, the treatment of coronary thrombosis is not within the scope of this discussion. However, thromboembolic phenomena are common after myocardial infarction, and are often the first symptom of a silent or nonrecognized infarct.[32] *The lung is the organ most frequently* involved, the ratio being four times as frequent as involvement of the extremities.[33] In cases of pulmonary embolism from an unrecognized source, one may see unnecessary femoral vein ligations. A careful case history, strengthened by an electrocardiogram will reveal the source of the embolus.

Prematurely ambulated or unrecognized cases of myocardial infarction seem to produce. (1) an increased number of peripheral arterial emboli,[32] and (2) ventricular aneurysms.[34] Regarding this frequent and disabling vascular accident as any other arterial occlusion, one would wish

to treat hypotension as early as possible.[35] The treatment consists of decreasing myocardial stress by absolute bed rest, and the use of anticoagulants Bed rest and hypotension may cause venous thrombosis in the lower extremities. Therefore, therapy should be maintained until the patient is fully ambulatory. The value of long-term anticoagulant therapy will be discussed later.

**Other Visceral Infarcts.** Emboli to spleen, kidney, and mesenteric arteries, represent specific clinical entities and may be diagnosed when the patient exhibits other thromboembolic phenomena. The diagnosis of this condition is suggested by: (1) a stitch in the left side with immobility of the left leaf of the diaphragm; (2) renal pain with microscopic hematurial and abdominal colic, and (3) distention, with bloody stools. Resection of gangrenous intestine is imperative.[36]

**Peripheral Arterial Thrombosis and Embolism.** Arterial thrombosis occurs at the level of trauma and at the level of inflammatory reactions of the wall or atheromatous plaques Sites of predilection would include all lesions which compress, constrict, or partially obstruct the vessel wall. Complete occlusion becomes clinically manifest usually when precipitated by acute hypotension, blood loss, or sudden increase in coagulability of the blood. Hemorrhage of the vessel wall from vasa vasorum, especially within atheromatous plaques, has been postulated by some workers[37] Certain segments of the peripheral arterial tree are subjected to repeated trauma and intermittent compression. These include: (1) the common iliac segment an inch below the bifurcation; (2) the superficial femoral artery at the proximal end of Hunter's canal, (3) the popliteal artery at the upper level of the popliteal muscle, and (4) the subclavian artery at the level of the first rib or a supernumerary rib.

Any diffuse vascular disease, especially arteriosclerosis, is more apt to localize at such levels. However, it may remain silent or hardly recognizable until the occluding thrombus supervenes. In a recent article,[38] the author advocated an emergency thromboendarterectomy in such patients. Sympathectomy and anticoagulant therapy are useful but may not save a limb when the lower femoral and popliteal level or the bifurcation of the aorta are involved. Whenever possible heparin should be given intra-arterially above the obstruction. In cases of arterial embolism, a period of an hour or so may be used to establish intensive conservative therapy such as sympathetic block, reflex heat, and heparin. However, the restoration of circulation by removal of the embolus is the ideal and most satisfactory procedure. This should be omitted only when too much time has elapsed between the vascular occlusion and the entrance of the patient to the hospital,[38] or if the patient is moribund. In a saddle embolus to the aorta, the patient may survive aspiration of the embolus through the two femoral arteries. However, the optimal procedure, consisting of a transperitoneal aortotomy, may not be tolerated by a patient in cardiac failure or fibrillation.

**Venous Thrombosis of the Extremities.** Certain clinical forms of this condition are frequent and easily-recognized. They will be described briefly since their management varies according to the stages and rates of progress.

*A. Superficial phlebitis* of saphenous segments in previously nonvaricose veins, is suggestive of early thromboangiitis obliterans If this is adequately and intensively treated, it may be arrested at the stage of migrating phlebitis. Saphenous vein ligation, bed rest, and anticoagulant therapy, are frequently employed. Such treatment is useless, and might even be harmful. The treatment of choice consists of: (1) complete abstinence from tobacco; (2) con-

tinuing ambulation with elastic compression, and (3) mild parenteral protein therapy with very small doses of typhoid vaccine or sodium thiosulphate.* These drugs act as nonspecific stressors through the pituitary-corticoadrenal axis. The disadvantages of using ACTH, and its impact on the clotting mechanism, will be discussed later. Large doses of sodium salicylate show a marked antiphlogistic effect, decrease of pain, and periphlebitic edema.

*B. Superficial saphenous phlebitis in varicose veins* requires ligation at the sapheno-femoral junction, with continued ambulation and elastic compression. If the thrombi are large, they can be evacuated or excised with the veins, immediately. Usually, however, one waits for the quiescence of the acute inflammation. Later, the entire vein can be stripped if it should recanalize. Roentgen ray therapy in doses not exceeding 80 R units has been helpful in decreasing periphlebitic edema and lymphocytic infiltration.[19]

*C. Superficial collateral phlebitis* is often mistaken for a saphenous phlebitis. Such patients either give the history, or show the characteristic collateral pattern, of an old deep venous occlusion In these patients, the flow in the veins is sluggish, the wall is thickened, and the wall shows low-grade, chronic inflammation Painful phlebitic patches are readily activated in the calf, in the thigh, or in collateral channels, of the abdominal wall, by slight trauma, sudden strain, or some systemic infections. Again, such patients require no bed rest, no anticoagulants, and certainly no saphenous vein ligation. It is interesting to note that the original deep venous thrombosis does not become activated Emboli from such a source have not been seen by the author. Large doses of salicylates, ade-

* The effect of intramuscular trypsin is likely to depend on the same mechanism

quate elastic compression, and Roentgen ray therapy, have been helpful. The problem of preventing recurrence is ever present. In selected cases, the veins can be stripped during a quiescent period. Long-term antibiotic therapy, helpful in chronic relapsing lymphangiitis, has not been of any definite help. In fact, the constant use of antibiotics in cases of acute phlebitis has never seemed indicated and may produce unnecessary sensitization reactions.

*D. Deep venous thrombosis involving subfascial veins.* In such thrombosis, the initial lesion is generally small, not readily detectable, and has a tendency to propagate and throw a pulmonary embolus. This is true whether the thrombosis starts in the plantar veins of the foot, in the muscle veins in the calf, in the plexuses formed by the posterior, anterior, or peroneal veins, in the adductor veins of the thigh, or in the veins of the pelvis and extrapelvic branches of the hypogastric vein. This is, in fact, the "phlebothrombosis" of Ochsner and De Bakey,[40] except that the same process, spreading to a confluence of trunks surrounded by lymphatic tissues such as the popliteal or inguinal area, now becomes an inflammatory periphlebitis (thrombophlebitis).[41] These situations call for immediate intensive anticoagulant therapy. Failure to institute immediate anticoagulant therapy, or to use sufficient dosage, protracts the disease and frequently results in chronic recurrent deep venous thrombosis with repeated embolization.[7] The disease is thus iatrogenic and only long, intensive anticoagulant therapy, combined occasionally with proximal vein ligation (preferably that of the vena cava), can arrest the disease.

In the authors' opinion, this recurrent condition is a typical example of failure of the clotting mechanism to respond to various forms of stress.[42] Such patients, when exposed to the stress of 25 mg. of intramuscularly adminis-

tered ACTH, exhibit no lengthening but possibly a shortening of the clotting time.[43] While the poor response exists, these patients may show attacks of recurrent thrombosis following stresses of daily life. Some of the stresses precipitating recurrence would include chilling, virous infections, mild trauma, prolonged bed rest, and the stresses of a surgical operation or childbirth.

**Axillary Venous Thrombosis.** This condition usually develops when the right arm is used for a sudden pull. Pain develops, swelling begins in the entire right upper extremity, there is a palpable cord in the axilla, and there is evidence of increased venous pressure in the cubital fossa. These lesions are aggravated and accentuated by exercise. Such a patient should be treated immediately, by elevation of the extremity at night, together with elastic compression and sympathetic block followed (but never preceded) by short intensive therapy with heparin. One week or more is the usual delay between onset and treatment. During that interval a collateral venous network has developed; the edema is more fixed, and exercise or active use brings on an intermittent claudication of the arm. This is caused by the sudden increase in venous pressure.

**Visceral Forms of Venous Thrombosis.** Such thrombi may occur in any organ, or at any site. Usually, however, they are secondary to ascending infectious thrombosis such as pylephlebitis after appendicitis. Likewise, they may occur in patients whose blood shows increased coagulability, as in polycythemia, or after splenectomy. In the latter instance, the combination of a ligature thrombus at the transected splenic vein, and the transient high platelet count, lead to splenic vein thrombosis. A detailed description of these various entities would lead us too far afield.

# III

## The Prevention of Thromboembolic Disease in Surgical Practice

One of the greatest deterrents to mass prophylaxis such as some institutions have established (dicumarol pre- and post-operatively) is that the incidence of post-operative thromboembolism is unknown. Statistics from the Charity Hospital in New Orleans, the Mayo Clinic, the Massachusetts General Hospital, and the University of Pennsylvania, have brought forth many interesting findings. However, the author and his co-workers have never felt that the hazards of drug-propylaxis are less than the disease it is trying to prevent.

The general status of the patient, prior to operation, is important from the standpoint of post-operative convalescence. The freely-ambulated patient, in good nutritional condition, in a normal electrolyte balance, and with a normal blood count, has a statistically lower chance of developing a blood clot than if the opposite factors prevail. In addition, we must not overlook the emotional status of the patient. Shortened clotting time is directly related to pre-operative anxiety. Adequate sedation, with barbiturates, notably diminishes this stress on the clotting mechanism. However, it must be noted that a higher incidence of thrombosis in such patients has by no means been proven. The dread of patients with a family history of thrombosis, may possibly be correlated with their vasomotor reactivity.[44]

If it were possible to determine which patients had a notably higher incidence of thromboembolic disease, mass prophylaxis could be avoided. The aged, cardiac, carcinomatous, diabetic, dehydrated, hyperlipemic, hypotensive, polycythemic, and previously-thrombotic patients, show a statistically higher incidence of thrombosis. Even in this group, one does not always feel the necessity of anticoagulant prophylaxis. Dicumarol prophylaxis was used in 6,705 women undergoing pelvic surgery during a ten year period at Free Hospital for Women in Brookline, Massachusetts.[43] A total of 102 cases of thromboembolism was observed (1.48%) which is no better than our incidence at St. Luke's Hospital on similar material, without dicumarol. The doses given were so small that they can only be regarded as token doses (100 milligrams every four days, starting the evening before the operation and continuing as long as the patient is hospitalized) Such prophylaxis, which is also practiced by some internists following cerebrovascular accidents, needs no prothrombin control and hardly affects the prothrombin level. *There is little danger of hemorrhage, but, in its long-term use, it creates an enslavement of the patient to his doctor and creates a continuous fear of impending disaster*

Another prophylactic regime requires a prothrombin level of 50% of normal, necessitating at least a weekly prothrombin determination Still another method requires levels between 30 and 15% of normal, the same as used in the therapy of acute thromboembolic disease.

Blood is capable of clotting with very little prothrombin present The customary determinations of prothrombin time do not actually measure the action of dicumarol on the clotting mechanism [1] Therefore, we have not felt it necessary to use coumarins or any other prothrombin depressant for prevention of thromboembolism.

Post-operative prophylaxis has been used on all patients with amputations of the lower extremity above the metatarsal level (lower leg, Callander, supracondylar, and midthigh). In all of these cases the common femoral vein was ligated at the time of amputation, as suggested by Ross Veal.[46] A high incidence of thromboembolism is noted in such aged sclerotic patients, post-operatively. The source of embolus is the stump of the ligated popliteal or superficial femoral vein. In our practice, prophylactic femoral vein ligations are not used in cases of hip fractures, after prostatectomies, or prior to combined abdominoperineal resections because it is our conviction that thrombi from the pelvic veins are a potent source of pulmonary embolism. In the series of Crutcher and Daniel, twenty-three out of fifty-five autopsies presented thrombi in the pelvic, upper abdomen, or even right auricle which accounted for a fatal pulmonary embolism.[47]

Clarence Gardner, and his associates, published convincing case reports of patients who developed the pulmonary embolism following vein ligation for thromboembolic disease.[48] Many other experiences of a similar nature could be cited. On our combined services of the Illinois Research, St. Luke's, and Hines Veterans Hospitals, prophylactic vein ligations have not been performed, nor do we advocate their use now except in amputations. Anticoagulant prophylaxis, however, has been carried out with heparin. This has been done mainly on patients whose heparin response is poor (Table I), or in those who have indicated that their response to stress is manifested by a shortening or non-lengthening of the clotting time. Therefore, we have given patients subcutaneous injections of heparin for three days prior to operation to fill up their stores of heparin, if: (1) they had previous thromboembolic episodes; (2) they had extensive carcinomatosis, (3) they were in cardiac fail-

ure, or (4) they had fibrillation. Patients treated in this manner respond much better to stress insofar as the clotting mechanism is concerned In addition, there is no danger of bleeding if the heparin is stopped the night before the surgical procedure.

# IV

## Methods of Treatment

We have indicated, in the foregoing pages, that effective therapy demands a clear recognition of the type and stage of thromboembolic disease with which one is dealing. It is fitting that a more detailed discussion be given some of these methods.

**Proximal Vein Ligation.** When a short, well-localized clot is excluded from the systemic circulation, it can not break loose. If this clot is due to the trauma of amputation, or to a well-defined stretch of muscle or tendon, superficial femoral vein ligation seems indicated It must be postulated that such a vein ligation leave minimal or no residual disability. This is not the situation in patients who have a clotting tendency, since the ligature thrombus may extend into the profunda or even break loose. A superficial femoral vein ligation can not protect a patient, from pulmonary embolism when it is done prophylactically after fractures of the hip or pelvis[49] Likewise, it provides no protection when done prior to prostatectomies or combined abdominoperineal resections.

Persuasive statistics have appeared from time to time in favor of prophylactic and therapeutic vein ligations.[50] Nevertheless, we limit the use of this operation to situations in which the patient can not be given heparin, or when in spite of adequate dosage of heparin, thromboembolic phenomena continue. Heparin can not be given patients with (1) a history of bleeding from the gastrointestinal tract;

(2) after operations on the central nervous system; (3) the urinary tract, and (4) in most instances of cardiovascular surgery. Other situations in which heparin may not be given are: (1) blood dyscrasias which lead to bleeding, and (2) in advanced hepatic or renal damage. When both femoral veins have been occluded, the only safe level for ligation is that of the vena cava. Thrombectomy, with vein-suture, recently has been revived,[30] and occasionally may be considered. Since it requires heparin therapy, however, it may not be possible to use it when it appears most desirable.

Ligation of the vena cava should be a routine emergency procedure after at least one massive pulmonary embolus, or in the presence of multiple emboli which anticoagulant therapy can not control. Vena cava ligation leaves the patient with a definite disability. It may lead to the permanent use of elastic hose, and may even result in postphlebitic ulceration, in induration, and in dermatitis. It must be emphasized, however, that many of the sequelae of vena cava ligation are due to inadequate early therapy leading to iliofemoral venous occlusions, and are not due to the ligation itself. We have always been extremely conservative in using this procedure and have records of only twelve such patients It should be remembered that simply stopping an inadequate dicumarol therapy may terminate the recurrent embolic phenomena.

Anticoagulant Therapy. *Heparin:* At the present time, there is no better anticoagulant than heparin. It is expensive and it can not be given orally or sublingually. All the macromolecular polysaccharides that have been synthetized for substituting heparin have either shown side effects such as platelet-clumping, or are too weak to use subcutaneously. Our laboratory has investigated two of these, i.e , treburon and thrombocid,[2] and is now studying dextran sulphate.

Indeed, there is promise of progress. However, until something better is discovered, one can not deprive patients of a drug whose action is so prompt, so dependable, and so predictable, as is heparin.

The response of patients to heparin varies, depending on many factors.[2,41] In addition, the response will vary even in the same patient, depending on the stage of the thromboembolic disease (Table II). In the acute phase, the patient is resistant to heparin. He has pain, edema, inflammatory reaction in the lymphatics, leucocytosis, eosinopenia, increased sedimentation rate, and the shortening of the heparin-retarded clotting time.[51] He may show water-retention just as in the first stage of stress following an operation.[2] This acute thrombotic state may be terminated by large doses of heparin. Not only should heparin be given immediately after recognition of the disease—but the size of the dose is of equal importance! The average starting dose is intermittent intravenous doses of 150 mg. of heparin every six hours (600 mgs. per day). Obviously, however, the state of nutrition, body weight, and a renal defect, may require modification of the dose. We have had to give as much as 1,000 mg. a day to a large, overweight, and decompensated patient to affect his clotting mechanism. We have never seen bleeding in the first stage of the disease. The study of hemorrhages occurring after heparin therapy would indicate that they occur when the thromboembolic disease enters a second stage. The second stage is the stage of resistance, when the natural defenses of the body come into play.

In this second stage, there is a sudden diminution of edema, slowing of pulse rate, defervescence, a rise in eosinophil count, and, most importantly, a sensitivity to heparin. The patient is clinically much better However, the dosage of heparin must be cut sharply to 200 to 300 mg. of heparin

a day, best given subcutaneously in 10 per cent solution. Subcutaneous heparin therapy has been investigated on our service[52] and 1 mg. of heparin per pound of body weight was found to be an average daily prophylactic dose. An average therapeutic dose was found to be 2 mg. per pound of body weight per day. It must be understood that these are only guiding principles, and the dose must be adjusted to the individual response of the patient.

The response of the patient may be measured by daily capillary coagulation times. Investigators agree that this is a crude bedside test. However, it avoids daily venipunctures, and can be performed by technicians, interns, nurses, and even by patients themselves. It directs anticoagulant therapy as is readily shown by capillary coagulation time curves. The level of eight to twelve minutes seems a safe, desirable coagulation time.[52] At one time, we thought that a plateau level of elevated coagulation times was desirable, and best obtained by depo-heparin (heparin retarded with a gelatin-dextrose mixture with or without vasoconstrictors). We are now convinced that intermittent, peak-effects are just as effective, and can be painlessly and less-expensively obtained by 10 per cent aqueous solutions. Twenty to 50 per cent concentrations would be even more desirable, but they are not readily available. Actually, 10 per cent solutions would be useful for both intravenous and subcutaneous administration Such a standardization would avoid confusion and mistaken dosages which occur with 1, 5, and 10 per cent solutions on the market.

More accurate control of heparin administration can be obtained by a venous clotting time sensitized with 1 microgram of heparin to each cubic centimeter of blood.[51] With this method, normal clotting times range from eleven to thirteen minutes, with a small scatter between ten and fifteen minutes[53] A sensitized clotting time of sixteen to

twenty minutes has been held to be optimal during therapy with heparin. This slightly-elevated clotting time protects against hemorrhage and seems to restore the normal antithrombotic mechanism of the blood. As has been stated elsewhere, heparin may not be *thrombolytic, but aids the* normal enzyme reactions of the body against the formation of thrombi. There is no need to double or treble the normal values of clotting time for effective anticoagulant therapy.

In the third stage of treated thromboembolic disease, the patient's clotting mechanism has been restored to normal. He now responds well to heparin, and if tested with ACTH, *he responds with a lengthening of the clotting* time.[53] In cases of venous thrombosis, it is wise to maintain a subcutaneous administration of heparin for at least three weeks, or until the patient can become ambulatory. *If heparin is stopped too early, or if the dosage is insufficient* to terminate the first acute stage, chronic thromboembolic disease results. This brings on periods of recurrence, and much disability due to persistent venous stasis.

Before the advent of anticoagulant therapy, patients with an iliofemoral thrombosis were kept at complete bed rest for four to six weeks, with their extremities elevated This led to the familiar slow convalescence and considerable postphlebitic sequelae. Recently, however, a new syndrome has developed—that of the ill-treated thromboembolic disease. It takes many months for such patients to overcome a smoldering disease, with recurrent attacks of thrombosis and pulmonary emboli. The common denominator in these patients has been the insufficient dosage of heparin. This has been emphasized by Jorpes[54] and Merz,[55] and has been observed repeatedly on our service.[2] It has also been the author's impression that prolonged small doses of dicumarol creates a disturbance of the clot-

ting mechanism. This may be because of increased fibrinogen production.[56] The situation is not unlike the one created by the widespread use of antibiotics in inflammatory disease. The latter situation results in suppression of clinical symptoms and various stages of resistance against the drugs used.

A patient's clotting mechanism subjected to long-term dicumarol therapy, cannot be simply expressed by a lowered prothrombin level.[4] In order to maintain a normal clotting equilibrium, the body has a whole set of enzyme systems and natural anticoagulants at its disposal. They function even in an acute stage of thrombosis. Otherwise, the entire circulating blood would clot. Instead, a local thrombus develops which, as Quick pointed out,[57] undergoes retraction and expresses a serum in which a rapid generation of thrombin occurs When the circulation is rapid, thrombin is quickly washed away and made innocuous by dilution. If the blood stream is stagnant, the nascent thrombin clots the blood surrounding the thrombus. This secondary clot becomes firmly attached to the first. It contains entrapped platelets, and will therefore retract. By numerous repetitions of this process, the thrombus is propagated. Anticoagulant therapy actively and efficiently inhibits the propagation of thrombi. There is increasing evidence that it aids the normal fibrinolytic mechanism of the body, which may also fluctuate during periods of stress.[58] Once the clot is quiescent and organized, no good can be expected from a prolonged stimulus created by depressing one of the clotting factors, namely, prothrombin, its precursors and accelerators. We have been unalterably opposed to long-term anticoagulant therapy, at least in surgical diseases. The evidence that it is clinically helpful has received valid criticism based on sound statistical data.[59]

Our practice has been to use massive, divided, intrave-

nous doses of 600 to 1000 mg. of heparin a day until the acute stage has subsided. This usually takes three to four days. Following this, with the appearance of heparin-sensitivity, subcutaneous doses of 200 to 300 mg. are given in two to three doses. These are kept up until the patient is normally active, but not more than six weeks. The doses are tapered off because rebound phenomena may occur.[3]

When the patient is first seen in a chronic recurrent *stage of the disease, management is much more difficult.* Too much heparin is not tolerated, and yet, emboli may occur in spite of sufficiently-increased clotting time or depressed prothrombin levels. If a short course of anticoagulant therapy does not control the disease, appropriate vein-ligation and *complete discontinuation of anticoagulants* is in order.

There is, finally, a *malignant* stage of the disease in which there is a continuous formation of thromboplastic substances such as occur in spreading carcinomas. Large doses of heparin by intravenous drip (300 to 600 mg. a day) may halt an acute thromboembolic episode. However, since the cause of the increased clotting tendency cannot be eliminated, further attacks are to be expected. In fact, the terminal phase of many cancers show pulmonary emboli. Such cases most certainly require a long-term anticoagulant therapy.

*Drug sensitivity to heparin:* A surprising number of patients show a sensitivity reaction to heparin. Some of these patients deny ever having previously received heparin. In a study of 256 patients receiving heparin, 8 per cent showed some degree of drug-sensitivity consisting of flushing of the face, bronchospasm, or gastrointestinal colic.[60] In addition, *the clotting time was greatly prolonged, and the eosinophils rose.*[42] This curious group of patients displays exten-

sive thromboses, needs heparin badly and reacts to it intensively. Frequently, they also demonstrate other allergies As a precautionary measure, it has been our custom to inject 1 cm. of a 1 per cent solution of heparin intravenously before any large doses are given. A coagulation time, determined before injection and ten minutes after injection, together with any clinical symptoms, rapidly reveals whether or not a hyperreactor is present.[61]

Thus far we have made no attempt to continue heparin therapy under the aid of antihistaminics or cortisone. Likewise, we have refrained from using heparin substitutes in such patients. Heparin, with its cofactor creates antiphlogistic, antihyaluronidase effects, and influences antigen-antibody reactions such as the Shwartzman phenomenon[62] Therefore, additional studies must be made to determine a safe anticoagulant therapy for such patients. Until such additional studies are made, discontinuation of heparin immediately, is indicated. Perhaps this will be one of the few instances where the coumarins may be employed.

*Hemorrhage due to heparin:* It has been mentioned previously that in an acute thromboembolic state, the patient tolerates massive doses of heparin. He is heparin resistant. Hemorrhage from heparin seems to occur: (1) either as a cumulative effect (more heparin being given than degraded or excreted), or (2) when the patient begins to respond normally to heparin after the acute stage subsides and the natural defense of the body is active. Such a state is preventable if clotting times are kept below eight to ten minutes of capillary and sixteen to twenty minutes of sensitized venous clotting time. Should hemorrhage occur, protamin sulphate is given intravenously, 1.5 mg. to each 1 mg of heparin being entirely suppressive. The effect of the protamine lasts about four hours and may have to be re-

peated. The author prefers it to toluidin blue which is given in doses of 2 mg. per kilogram of body weight, intravenously, over a period of two hours, in 500 cc. of physiologic saline solution.

The action of these two drugs is prompt, and their administration is urgent. Uncontrolled hemorrhage produces a hemorrhagic state, characterized by low platelet count and the appearance of fibrinolysins. This state is not neutralized by protamine or toluidin blue. Blood transfusions are the best therapy in such instances, but they may increase hemorrhage if not carefully crossmatched.[63]

Although heparin is used extensively on our service (approximately 100 to 150 patients per year), only one massive hemorrhage was encountered. This was due to overdosage, combined with a paravertebral block, resulting in a huge retroperitoneal hematoma which was followed by cord symptoms.[12]

*Heparinoid substances:* Synthetic, sulfurated polysaccharides prolong clotting time. However, all of the ones which we have tested thus far have side-reactions. Paritol has not been used. Thrombocid and treburon have been given extensive clinical, and some experimental trial on our service.[7] Alopecia and diarrhea were observed. Platelet agglutination, leading to temporary thrombocytopenia and platelet thrombi in lung, kidney, and liver, may occur.[64] Recently, dextran sulphate has been received from England and has been shown to have good anticoagulant activity after individual injections. Whether two to three weeks of intensive anticoagulant therapy will lead to side-reactions is not known to us However, a joint British report is favorable.[65]

At the present time, one cannot deprive patients of the safe, dependable, though expensive, heparin. The synthetic preparations have all been produced at a cost which is less

than that of heparin. One must postulate that the synthetic, heparinoid substances can be given painlessly into subcutaneous tissue without local or general reactions. Further, that they can be concentrated into small volume and be as nonallergenic as possible. The synthetic preparations have not as yet attained this status.

*Prothrombin depressants.* The use of dicumarol and its substitutes such as tromexan, cyverine, and phenylindanedione, is widespread. Many internists and general practioners have used it to such an extent that it has led surgeons to use the same drugs in venous thrombosis of the extremities, or other thromboembolic diseases requiring long anticoagulant therapy. Long-term anticoagulant therapy is defined as treatment on an out patient basis for a period of four weeks or longer.[4] Our attitude toward the use of these drugs for a short term or long term, is based on experience with 400 patients[40] and an analysis of the more recent literature.

All of these drugs seem to act by inhibiting the formation of prothrombin in the liver. It is possible that activator or accelerator substances are involved. The accepted, ideal prothrombin level, at which clotting should not occur nor should hemorrhage develop, is around 20 per cent of normal. Schnur[39] has recently pointed out that this goal can be obtained in only 44 per cent of the cases, and that the remaining 66 per cent are in a non-protective or hemorrhagic zone. The patient, however, whose prothrombin production is only slightly depressed, may show a shortened clotting time.[41] Our first experience with this was with a patient whose prothrombin levels dropped very slowly because of insufficient dosage. The therapeutic level was not reached until the ninth day. Until the seventh day, the sensitized clotting times were falling from an initial level of twenty-eight minutes (sensitized with 4 gamma of

heparin) to the low level of nine minutes. We interpreted this phenomenon as being due to the stimulating effect of small doses of dicumarol on fibrinogen production in the liver, as suggested by the work of Irish and Jaques.[56]

It must be remembered that most patients are undertreated with dicumarol. Therefore, iatrogenic chronic recurrent thromboembolic disease develops. This can only be helped by complete cessation of dicumarol therapy. During the time of withdrawal, a short, intensive course of heparin therapy, lasting from two to three weeks, should be instituted.

Specially manned and equipped institutions, with considerable experience in administering dicumarol or its substitutes, are able to maintain a prothrombin percentage of about 20 per cent of normal. Nevertheless, patients may bleed massively with a higher level than 20 per cent, and throw emboli at a lower level. This is particularly true if the thrombus is dislodged from the heart to the arterial tree as against being released from the vein to the pulmonary artery.[66] Four deaths have been reported from hemorrhage during the administration of dicumarol, all four patients having "safe" levels of prothrombin.[67] This points to the fact that the present laboratory control of dicumarol is still highly controversial. Uniform methods and readily-reproduceable data, are still not in general use. It is even doubtful whether the so-called "prothrombin" time is not just an accelerated clotting time, and does not measure prothrombin alone. Since we are partial to the heparin-clotting time, it might be well to consider using this simple method to follow the effect of dicumarol therapy.[61,63] Cases have recently been reported in which prothrombin levels were below 65 per cent of normal, and still showed increased resistance to heparin On the other hand, hemorrhage has been observed with a "safe" prothrombin level,

the blood showing simultaneous hypocoagulability by a heparin-retarded clotting time.[69]

The results seem to indicate that reliance on prothrombin levels does not give one a full account of the state of the clotting mechanism. In fact, it is reasonable to assume that any depression of one factor in the chain-reaction of clotting would bring about a compensating, counter-reaction to restore the balance. Obviously, this same objection could be raised against heparin, except that this drug inhibits so many phases of coagulation, or perhaps all of them.[70] There is still need of a dependable test to indicate that the state of the clotting equilibrium is precarious Any small stress, such as fright, anxiety, chill, anesthesia, trauma, or operation, can deplete the natural anticoagulant reserve of the body. One is not aware that patients who have been subjected to months and even years of anticoagulant therapy have such a clotting tendency.[4] It is true that a coronary occlusion may have occurred at the site of a stenotic, atheromatous coronary artery, requiring short-term anticoagulant therapy to prevent thromboembolic phenomena in the convalescent period. There is nothing to indicate however that such a patient's clotting mechanism is in any way disturbed. Long-term anticoagulant therapy disturbs it to an extent that it can hardly be safely withdrawn both for psychological reasons and because a long-term prothrombin depression evokes homeostatic regulation. Cerebral infarcts often reveal no cerebral artery thrombosis.[5] In addition a recent analysis of the incidence of coronary thrombosis in 235 patients with myocardial infarcts revealed, at autopsy, an absence of clotting in 57 per cent of the cases[71] In other words, 1,358 of 2,351 patients, if they had been placed on long-term anticoagulant therapy, would have received anticoagulants for a clot which could not be demonstrated at autopsy.

For the above-mentioned reasons, we are unalterably opposed to long-term anticoagulant therapy, except in the malignant phase of the disease, which is a state of decompensated clotting mechanism. A short-term intensive therapy, using heparin, is our method of choice for treatment and for the elimination of an acute propagating process.

**Hemorrhage Due to Coumarins and other Depressants of Prothrombin.** In certain situations, the surgeon may wish to restore prothrombin concentration to a "safe" level quite rapidly, or, he may have to operate in the presence of hemorrhage. Generally speaking, if there is no hemorrhage, discontinuation of the drug is the optimal procedure. From four to eight days were allowed to elapse before dental extraction, and with this precaution no bleeding was encountered.[4] When major surgery, either an urgent laparotomy or vena cava ligation needs to be done, Vitamin $K_1$ in 500 mg. oral doses or the intravenous emulsified preparation of Vitamin $K_1$ in 250 mg. doses restores the prothrombin level in four to eight hours to a normal or near-normal level. However, these measures, added to transfusion of freshly stored blood may bring on a propagation or recurrence of the disease for which it was originally given. Such a case was reported by Fowler and the author early in our experience with dicumarol.[41]

As in the case with heparin, such hemorrhages may result in a state of hemorrhagic shock in which the low prothrombin level is not the only factor, and where great care must be taken that the transfused blood is not an additional source of hemorrhage.[63]

**Enzyme Therapy.** Spontaneous lysis of clots occurs both in vitro and in vivo. MacFarlane and Biggs[72] have studied a number of factors which favor fibrinolysis. Tagnon *et al.*[73] reported fibrinolysis in patients who were in hemorrhagic shock. They also produced this phenomenon ex-

perimentally. Both prothrombin and fibrinogen levels dropped. Such a phenomenon frequently occurs after pulmonary embolism, or after operations. We have commented previously on the danger of too much anticoagulant therapy in this phase of thromboembolic disease because it may lead to hemorrhage.[2] Coon and Hodgson have recently pointed out that fibrinolysis occurs after surgical operations, and explains a hemorrhagic diathesis as being occasionally encountered.[74]

These and other observations indicate an existing mechanism for the natural dissolution of clots. This has excited the imagination of several investigators to utilize such an enzyme-reaction for thrombolysis. Innerfeld *et al.* advocate intravenous trypsin for the treatment of thrombosis.[75] More recently, an intramuscular method of administration has been substituted. Wright *et al.*[76] denied beneficial effect of such a procedure, and pointed to its dangers. At an early date, we received some material for clinical trial and gave doses of 100,000 to 150,000 units dissolved in 500 cm. of physiologic saline solution once or twice a day, by slow intravenous drip Chills, fever, and evidence of parenteral protein reaction, were frequent. Phlebitic edema was favorably influenced. However, in the doses administered, there was no detectable change in the clotting mechanism. The clinical response of these patients forcibly reminds one of the reactions of patients suffering from thromboangiitis obliterans, to whom small doses of typhoid vaccine were given.[77] Unquestionably, the degradation products of protein, particularly those of fibrin, may given rise to a series of enzymatic reactions brought about by "trypsin-shock."

However, this seems like a round-about, and not well-controlled way to activate fibrinolysin.

Another approach to this problem consists of using minute amounts of tissue-juice (thromboplastin) to activate

profibrinolysin, sometimes referred to as proplasmin. Tagnon and Palade[78] isolated a plasmin activator from lung tissue, which may be thromboplastin itself. In order for plasmin (fibrinolysin) to become activated, it needs contact with extravascular organs. Experimental observations indicate that minute amounts of thromboplastin, infused intravenously, create: (1) a prolongation of clotting time; (2) a prolongation of prothrombin time of diluted and undiluted plasma; (3) a decrase in platelets, and (4) a prolongation of thrombin clotting time. Significantly, these effects occurred before the concentration of fibrinogen dropped.[79]

What is needed, of course, is a simple clinical test for fibrinolytic activity, or for the presence of increased amounts of anti-fibrinolysin. Our laboratory has investigated a number of these tests, ranging from simple qualitative tests to spectroscopic ones, and hopes to contribute a test of simply measurable fibrinolytic activity in the near future. It is becoming clear that many forms of stress, such as trauma, Roentgen-ray therapy, surgical operation, and ACTH increase proteolytic activity.[80] Cliffton has recently reported the intravascular use of fibrinolysin to dissolve clots "in vivo."[81] The development of this idea is awaited with great interest. However, the limitations and hazards of this method are as yet unknown.

In the meantime, those who believe in intensive heparin therapy, particularly when administered regionally, proximally to an arterial, and distally from a venous clot, are practicing fibrinolytic therapy. Heparin was originally thought to inhibit fibrinolysis. More recent reports, however, suggest that heparin facilitates fibrinolysis by allowing the natural enzymatic system to attack the clot. Halse[82] believes it is a potent fibrinolytic agent, although not all preparations seem to contain the same amount of fibrinolytic activity.

On our service, we have injected heparin intra-arterially above any fresh clot when a pulsating femoral or brachial artery was accessible. We have seen a remarkable restoration of continuity in two patients, although it should be admitted that this occurs spontaneously. In suitable patients with deep venous thrombosis, we have cannulated the short saphenous vein at the ankle, and used a heparin drip infusion (100 mgs to 1000 cc. of physiologic saline solution) when the patient was seen quite early and when immobility for four to five days was not too inconvenient. An impression, rather than an evaluation, is that unless the clot is quite fresh, it will not be lysed. A clot well along in the process of organization could hardly be expected to dissolve Nevertheless, the attempt to administer heparin regionally, exposing the clot to a higher concentration, is certainly worth the effort.

Paravertebral Sympathetic Block. It has been assumed for a long time that acute arterial and venous occlusions are associated with intense vasospasm of the affected vessel, and the collateral bed. In arterial embolism and thrombosis, we have advocated its early systematic use.[83] Ochsner and De Bakey gave uncontrovertible evidence that in experimental venous thrombosis the plethysmographic pulse waves can be greatly augmented after sympathetic paralysis[84] It has become common clinical experience that a well-performed paravertebral block will transform a cold, pale, or cyanotic extremity into a warm, pink one without necessarily restoring the pulse. However, it is our feeling that arterial occlusions require a sympathetic block but venous occlusions need them only when the extremity shows evidence of vasospasm This is present when pulses are weaker or absent, the skin cyanotic and moist. The majority of venous thrombosis, especially those in the calf, produce a warm extremity with bounding pulses and no evidence of vasospasm. It is

the author's feeling that the infiltration of the vascular sheath in the groin with periphlebitic edema is a potent source of vasospasm. He further feels that the calf muscle thrombosis only produces vasospasm when associated with severe pain and muscle spasm.

With the widespread use of anticoagulants, great care should be exercised in avoiding paravertebral blocks while the patient is on anticoagulant therapy. Lilly and Lee[85] reported numerous, and sometimes fatal cases of hemorrhage when such a combination was used. On our service, we have had at least two massive hemorrhages. In one patient, a dorsal sympathectomy was performed with almost insurmountable difficulties. The difficulties were brought about because daily sympathetic blocks, combined with anticoagulant therapy, produced a cement-like calcified, retropleural hematoma.

Myogenic spasm of the occluded vessel, especially that of a muscular artery, like the femoral, will not respond to sympathetic block. The exposed artery visibly hugs an embolus and is contracted both above, but more often below, the occlusion.[86]

**Emergency Surgical Procedures.** Sympathectomy may save a critically ischemic extremity in an acute arterial occlusion. *This is especially true if thromboendarterectomy or embolectomy are not feasible.* It has not been our custom to preform sympathectomies following venous occlusions, neither in the subacute or the chronic stage, unless a causalgic type of pain persists in which either repeated blocks or preferably sympathectomy are of great benefit.[87] Since chronic late stages of thromboembolic disease are not within the scope of this report, I shall not discuss late disabilities and their treatment except to point to an inclusive discussion of Ensenat on the subject.[88]

**Combination of Methods.** The specific treatment of thromboembolic disease is anticoagulant therapy. There are, however, several good reasons why additional methods should be employed. The hemodynamic effects of thrombotic occlusion, causing increased resistance in the collaterals, call for sympathetic paralysis. We have already warned against using the two methods simultaneously. Proximal vein ligation or venous thrombectomy should certainly be followed by anticoagulants—unless anticoagulants are contraindicated. The use of reflex heat in the form of heat cradles to the abdomen, or direct heat to a calf muscle thrombus with hard, spastic flexor muscles, is obviously useful. However, an ischemic leg should never be heated or refrigerated unless amputation is planned but simply wrapped in absorbent cotton.

# V

## Discussion

THROUGHOUT this report we have tried to show that many of the clinical syndromes which are regarded and treated as being due to thromboembolic disease are really due to arterial stenoses, with a sudden occlusion due to hemodynamic conditions or vascular changes in the wall. To this group belong the cerebral and myocardial infarcts and the great number of peripheral arterial thromboses representing a critical phase of arteriosclerosis. There is no evidence to show that the clotting mechanism is responsible for the appearance of the occlusion, nor that it means a permanent clotting tendency which has to be combated with long-term anticoagulant therapy. These vascular occlusions derange the clotting mechanism temporarily. This may be because the small occluding thrombus sets up a chain-reaction of propagating thrombi.[57] On the other hand, it may occur, because the stress of the occlusion, including hypotension, fright, pain, and other stressful conditions, imposes a response of the clotting mechanism with which some patients are unable to cope. For some years, our group has been engaged in the study of the response of the clotting mechanism to various forms of stress.[42,43] We are firmly convinced that by studying the effect of ACTH on a heparin-retarded clotting time, one can separate a normal clotting mechanism from one which is in danger of failure. There are many observations to show that operative results in a fluctuation of clotting factors in the p

tive period.[39] We are here primarily interested in surgical stress. However, one can show, with a heparin-retarded clotting time, that the same triphasic response which Selye has named the "adaptation syndrome," becomes manifest after coronary thrombosis.[40]

The author, with M. T. Voigt,[41] found that young, healthy individuals responded with a prolongation of clotting time four hours after 25 mgs. of ACTH. We also found that a prolongation of clotting time was the normal response, together with the "third day eosinophilia" after major operations Richard Warren *et al.*[30] duplicated the postoperative thrombocytopenia with 80 mgs of ACTH, even though they could not reproduce the thrombocytosis of the second week. It is our belief that a microstress, produced with 25 to 40 mgs. of ACTH, gives a fair picture of what will happen postoperatively since patients with known acute thrombosis, or with known thrombotic tendencies, failed to show a lengthening, and in some instances manifested a shortening, of clotting times. Cosgriff *et al.*[41] described patients who developed thromboembolic phenomena while receiving ACTH or cortisone (10 out of 175 patients, 5.7 per cent). Their patients must have belonged to this endangered group, since most patients show a significant increase in heparin-like substances in the blood after ACTH [42]

There are patients in whom a thrombotic episode, occurring at a site of vascular stenosis, stasis, or trauma, is followed by a failure of the clotting mechanism to respond with thrombolysis, or at least with a lack of inhibition of propagating thrombosis. These patients are in urgent need of heparin Most patients, after a single episode, especially in the arterial system, give no indication that their clotting mechanism has failed Another group of patients, however, has a defect in the clotting mechanism. Each child-

birth and/or operation is followed by thrombosis. They are like the decompensated cardiac, or the uncontrolled diabetic patient. They need heparin during every stress. We have gathered evidence which suggests that a short pretreatment with heparin may fill up the heparin stores of these patients and allow them to withstand stress without consecutive thrombosis. Perhaps their chronic recurrent thromboembolic disease has been produced, or at least protracted, by insufficient anticoagulant therapy. Most long-term anticoagulant therapy is insufficient!

Two methods have been advocated to detect such patients. The first, is the ACTH test for clotting response. For a large general service it is easier to use serial daily clotting times and the character and shape of the clotting curve may warn of impending thrombosis. Bergquist[95] has shown, even with a crude capillary coagulation time, that 16 per cent of patients showed a shortened coagulation time. He heparinized these patients only to restore the normal coagulation time. For some years we have made serial determinations of eosinophil counts and venous coagulation times, *sensitized* with 1 microgram of heparin. When the normal pattern of fall, rise, and return to preoperative clotting time, has been absent, heparin is given prophylactically in small doses. This is done, not to double or treble the initial clotting time, but to obtain the customary normal rise of 10 to 15 per cent above preoperative levels. The third to fifth day seems to be most importa[illegible] from the standpoint of the initial small thrombus. H[illegible] ever, it is well known that the clinically manifest [illegible] which grew from a small beginning, s[illegible] a later [illegible] ance. On a series of patients still to [illegible], a [illegible] nation on the third and fifth post[illegible], seems permit sufficient protective action

We believe, then, in selective, [illegible]

phylaxis since the incidence of postoperative thrombosis is between 1 and 2 per cent. Medical patients, in bed, show an incidence of 2.1 per cent. However, the incidence after leg injuries is much higher than this, Bauer's series[94] showing up to 12 per cent. This fact, often overlooked by industrial and insurance departments, has been observed by us in many instances We are inclined to believe that, in the absence of a growing hematoma, such patients need prophylactic doses of heparin. Injuries to the calf and thigh, with and without fractures, need special attention.

There has been much argument about the method of administering heparin. We have almost abandoned the intravenous drip, and reserve it only for regional intra-arterial heparinization during arterial graft or endarterectomy.[95] In the latter instances, it is used to prevent clotting in a non-pulsatile arterial segment with low blood pressure and sluggish flow. Also, it may be the only way to keep the blood from clotting in the malignant phase of thromboembolism, with multiple recurrent venous thromboses, in the presence of spreading malignancy. Regional venous heparinization has been utilized by Blakemore[96] to protect his portocaval shunts. A continuous regional drip also may be occasionally helpful in a deep venous thrombosis, introduced through the short saphenous vein.

Generally speaking, however, the intermittent intravenous administration of 100 to 150 mgs. of heparin has been our choice to control acute venous thrombosis. Such a method produces peaks and dips in the clotting curves, but there is no real proof that a plateau type of steadily elevated clotting-time is preferable. Bauer *et al.*[97] demonstrated that a high concentration of heparin, exerting its effect on the loose, early clot, is an important consideration. The author agrees with Bauer's findings. However, Bauer's early intensive dosage, advocated for five to

birth and/or operation is followed by thrombosis. They are like the decompensated cardiac, or the uncontrolled diabetic patient. They need heparin during every stress. We have gathered evidence which suggests that a short pretreatment with heparin may fill up the heparin stores of these patients and allow them to withstand stress without consecutive thrombosis. Perhaps *their chronic recurrent* thromboembolic disease has been produced, or at least protracted, by insufficient anticoagulant therapy. Most long-term anticoagulant therapy is insufficient!

Two methods have been advocated to detect such patients. The first, is the ACTH test for clotting response. For a large general service it is easier to use serial daily clotting times and the character and shape of the clotting curve may warn of impending thrombosis. Bergquist[95] has shown, even with a crude capillary coagulation time, that 16 per cent of patients showed a shortened coagulation time. He heparinized these patients only to restore the normal coagulation time. For some years we have made serial determinations of eosinophil counts and venous coagulation times, sensitized with 1 microgram of heparin. When the normal pattern of fall, rise, and return to preoperative clotting time, has been absent, heparin is given prophylactically in small doses. This is done, not to double or treble the initial clotting time, but to obtain the customary normal rise of 10 to 15 per cent above preoperative levels. The third to fifth day seems to be most important from the standpoint of the initial small thrombus. However, it is well known that the clinically manifest clot, *which grew from a small beginning, shows* a later appearance. On a series of patients still to be reported, a determination on the third and fifth postoperative day seems to permit sufficient protective action against thrombosis.

We believe, then, in selective, and not massive, pro-

phylaxis since the incidence of postoperative thrombosis is between 1 and 2 per cent. Medical patients, in bed, show an incidence of 2.1 per cent. However, the incidence after leg injuries is much higher than this, Bauer's series[94] showing up to 12 per cent. This fact, often overlooked by industrial and insurance departments, has been observed by us in many instances We are inclined to believe that, in the absence of a growing hematoma, such patients need prophylactic doses of heparin. Injuries to the calf and thigh, with and without fractures, need special attention.

There has been much argument about the method of administering heparin. We have almost abandoned the intravenous drip, and reserve it only for regional intra-arterial heparinization during arterial graft or endarterectomy.[95] In the latter instances, it is used to prevent clotting in a non-pulsatile arterial segment with low blood pressure and sluggish flow. Also, it may be the only way to keep the blood from clotting in the malignant phase of thromboembolism, with multiple recurrent venous thromboses, in the presence of spreading malignancy. Regional venous heparinization has been utilized by Blakemore[96] to protect his portocaval shunts. A continuous regional drip also may be occasionally helpful in a deep venous thrombosis, introduced through the short saphenous vein.

Generally speaking, however, the intermittent intravenous administration of 100 to 150 mgs. of heparin has been our choice to control acute venous thrombosis Such a method produces peaks and dips in the clotting curves, but there is no real proof that a plateau type of steadily elevated clotting-time is preferable. Bauer *et al.*[97] demonstrated that a high concentration of heparin, exerting its effect on the loose, early clot, is an important consideration. The author agrees with Bauer's findings. However, Bauer's early intensive dosage, advocated for five to

six days to abort the process, has given us a high percentage of recurrence. For this reason, after three days of intravenous saturation of the patient, we continue with intramuscular heparin in two to three doses of 100 mgs. in 10 per cent aqueous solution. It is inadvisable, however, to begin with intramuscular or subcutaneous doses since such a procedure gives a high rate of propagation or recurrence. In addition, fatal pulmonary emboli are encountered in the astounding figure of 6 per cent.[97] This, again, illustrates our reason for emphasis on insufficient dosage.

We have abandoned the use of heparin in retarding media (depoheparin[52]), because it is painful, expensive, and the plateaus are unimportant. Intravenous use is wasteful, since 40 to 60 per cent of heparin is excreted in the urine after 100 to 150 mgs. of intravenous heparin injection.[98] However, as shown by the excretion curves of Merz,[55] a sudden improvement in the course of the disease reflects itself in increased excretion, and, during the acute stage much heparin is bound, neutralized, or degraded. Thus, if a simple method for quantitative heparinuria was available, it would be useful to control the dosage.

If the veins of the extremities are involved, after three days of intravenous and about four days of intramuscular or deep subcutaneous administration of heparin, a patient can ordinarily be ambulated with suitable elastic compression. Under no circumstances, however, should the heparin be stopped. The patient, or his family, can be taught to give 10 per cent aqueous heparin in 1 cm doses once or twice a day subcutaneously. By this time, controls with clotting times are unnecessary. Depending on the extent and rapidity of spread, this ambulatory heparin therapy is maintained for an additional two weeks. We have always regretted stopping the ambulatory heparin dosage after one week, because of the high rate of recurrence—about

50 per cent. This may occur immediately, or after a few weeks, as if the disease had not "burned out." In a previous report we used Francis Moore's[99] excellent term "failed convalescence," when this occurred.

This report can only give our mode of procedure as of the spring of 1955. New procedures may readily outdate this one, and this is desirable since it denotes progress. It should be re-emphasized that anticoagulants are used for prophylaxis and treatment in all patients except those who have had a massive infarct, and in whom anticoagulants are contraindicated. Although surgeons have always had considerable interest in thrombosis, the ratio of non-surgical to surgical cases is 8:1[100] Prophylactic and therapeutic superficial femoral vein ligations are no longer used with the former frequency. Sympathetic blocks have a dominant influence on arterial, but less important effect in venous thrombosis Favoring or stimulating the natural fibrinolytic mechanisms of the body seems the immediate task before us.

# VI

## Summary

Thromboembolic disease has been shown in this report as having acute, chronic, chronic recurrent, and malignant phases. It has also been shown to appear under different clinical forms, producing cerebrovascular accidents, vertebral vein thrombosis, pulmonary embolism, coronary thrombosis, visceral infarct, peripheral arterial thrombosis and embolism, venous thrombosis of the upper and lower extremities, and venous thrombosis of the viscera.

Prophylaxis and treatment have been discussed, evaluating proximal vein ligation, anticoagulant therapy with heparin, heparinoids and prothrombin depressants, enzyme therapy, paravertebral sympathetic block, and emergency surgical procedures. Combination of these methods has been described.

We have favored the use of anticoagulants for prophylaxis and treatment in all patients, except those in whom such treatment has failed to prevent an infarct, and in whom they were not feasible.

Finally, it was stressed that long-term anticoagulant therapy, carried on for months or years, has no place in the treatment of patients whose clotting mechanism is undamaged.

TABLE I

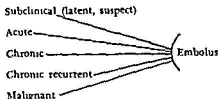
FACTORS INFLUENCING HEPARIN TOLERANCE

| *Decreased Response* | *Increased Response* |
|---|---|
| Advanced age | Youth |
| Acute thrombosis (first phase) | Acute thrombosis (second phase) |
| Postoperative state (first phase) | Postoperative state (second phase) |
| Hemoconcentration | Traumatic } shock, |
| Polycythemia | Hemorrhagic } fibrinolysis |
| Thrombocytosis | Thrombocytopenia |
| Digitalis (toxic doses) | Hepatic damage |
| Hyperlipemia* | Renal damage |
| Carcinomatosis | Hypoprothrombinemia |

* All other factors observed and studied by ourselves; this one is listed on the basis of Duncan's report (*Gastroenterology*, 17.360, 1951).

TABLE II

THE SPONTANEOUS COURSE OF THROMBOEMBOLIC DISEASE



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*This Book*

# THROMBOEMBOLIC DISEASE

*By*

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